**Title:** Hydrogel Spacer use During Radiotherapy for Prostate Cancer

<table>
<thead>
<tr>
<th>Populations</th>
<th>Interventions</th>
<th>Comparators</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Individuals:</td>
<td>Interventions of interest are:</td>
<td>Comparators of interest are:</td>
<td>Relevant outcomes include:</td>
</tr>
<tr>
<td>• With prostate cancer who are undergoing radiation therapy</td>
<td>• Perirectal hydrogel spacer</td>
<td>• External beam radiotherapy</td>
<td>• Symptoms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Quality of life</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>• Treatment-related morbidity</td>
</tr>
</tbody>
</table>

**DESCRIPTION**

For low- or intermediate-risk prostate cancer, radiation therapy is an option. Because the rectum lies in close proximity to the prostate, the risk of rectal toxicity is high. One approach is to push the rectum away from the prostate, increasing the space between the 2 and reducing the radiation dose to the rectum. A variety of biomaterials, including polyethylene glycol hydrogels (eg, SpaceOAR System) have been evaluated as perirectal spacers.
Objective
The objective of this evidence review is to determine whether the use of a perirectal hydrogel spacer in patients with prostate cancer who are undergoing external beam radiation therapy improves the net health outcome.

Background
Prostate cancer is a complex, heterogeneous disease, ranging from microscopic tumors unlikely to be life-threatening to aggressive tumors that can metastasize, leading to morbidity or death. It is the second most common cancer in men, with over 1 in 10 men diagnosed with prostate cancer over their lifetime. Cancer is typically suspected due to increased levels of prostate-specific antigen upon screening. A digital rectal exam may detect nodules, induration, or asymmetry, and followed by an ultrasound-guided biopsy with evaluation of the number and grade of positive biopsy cores.

Clinical staging is based on the digital rectal exam and biopsy results. T1 lesions are not palpable while T2 lesions are palpable but appear to be confined to the prostate. T3 lesions extend through the prostatic capsule, and T4 lesions are fixed to or invade adjacent structures. The most widely used grading scheme for a prostate biopsy is the Gleason system. It is an architectural grading system ranging from 1 (well-differentiated) to 5 (poorly differentiated); the score is the sum of the primary and secondary patterns. A Gleason score of 6 or less is low-grade prostate cancer that usually grows slowly; 7 is an intermediate grade; 8 to 10 is high-grade cancer that grows more quickly. A revised prostate cancer grading system has been adopted by the National Cancer Institute and the World Health Organization. A cross-walk of these grading systems are shown in Table 1.

Table 1. Prostate Cancer Grading Systems

<table>
<thead>
<tr>
<th>Grade Group</th>
<th>Gleason Score (Primary and Secondary Pattern)</th>
<th>Cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>6 or less</td>
<td>Well-differentiated (low grade)</td>
</tr>
<tr>
<td>2</td>
<td>7 (3 + 4)</td>
<td>Moderately differentiated (moderate grade)</td>
</tr>
<tr>
<td>3</td>
<td>7 (4 + 3)</td>
<td>Poorly differentiated (high grade)</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
<td>Undifferentiated (high grade)</td>
</tr>
<tr>
<td>5</td>
<td>9-10</td>
<td>Undifferentiated (high grade)</td>
</tr>
</tbody>
</table>

Regulatory Status
In October 2014, SpaceOAR® (Augmenix, a subsidiary of Boston Scientific) was cleared by the FDA through the De Novo process (DEN140030). "SpaceOAR System is intended to temporarily position the anterior rectal wall away from the prostate during radiotherapy for prostate cancer and in creating this space it is the intent of SpaceOAR System to reduce the radiation dose delivered to the anterior rectum."
POLICY
A. Hydrogel spacer use during radiotherapy for prostate cancer is considered experimental / investigational.

B. Use of a hydrogel spacer for any other indication is experimental / investigational.

RATIONALE
This policy was created with a search of the MEDLINE database through November 24, 2019.

Evidence reviews assess the clinical evidence to determine whether the use of technology improves the net health outcome. Broadly defined, health outcomes are the length of life, quality of life (QOL), and ability to function—including benefits and harms. Every clinical condition has specific outcomes that are important to patients and managing the course of that condition. Validated outcome measures are necessary to ascertain whether a condition improves or worsens; and whether the magnitude of that change is clinically significant. The net health outcome is a balance of benefits and harms.

To assess whether the evidence is sufficient to draw conclusions about the net health outcome of technology, 2 domains are examined: the relevance, and quality and credibility. To be relevant, studies must represent one or more intended clinical use of the technology in the intended population and compare an effective and appropriate alternative at a comparable intensity. For some conditions, the alternative will be supportive care or surveillance. The quality and credibility of the evidence depend on study design and conduct, minimizing bias and confounding that can generate incorrect findings. The RCT is preferred to assess efficacy; however, in some circumstances, nonrandomized studies may be adequate. RCTs are rarely large enough or long enough to capture less common adverse events and long-term effects. Other types of studies can be used for these purposes and to assess generalizability to broader clinical populations and settings of clinical practice.

Hydrogel Perirectal Spacer
Clinical Context and Therapy Purpose
Early localized prostate cancer can usually be treated with surgery and radiotherapy, although active surveillance may be adopted in men whose cancer is unlikely to cause major health problems during their lifespan or for whom the treatment might be dangerous. In patients with inoperable or metastatic disease, treatment consists of hormonal therapy and possibly chemotherapy. Treatment decisions are based on the anatomic extent of the lesion, the histologic grade from biopsy, and serum prostate-specific antigen level. Other factors in treatment decisions are expected outcomes, potential complications, along with medical condition, age, comorbidities, and personal preferences. For patients with clinically localized low-risk cancer (no palpable tumor and prostate-specific antigen of 10 or less), active surveillance is an option. Definitive therapy with radical prostatectomy or radiation therapy (RT) with external beam and/or brachytherapy is also an option for low- or intermediate-risk disease. Dose escalation of RT improves cancer outcomes but also increases the risk of urinary or rectal toxicity. Image-guided RT and intensity-modulated RT may be used to limit margins and reduce toxicity but because the rectum lies in close proximity to the prostate, the risk of rectal toxicity
remains high. Hypofractionation that reduces the number of treatments, dose-escalation, and salvage RT protocols can be particularly prone to rectal toxicity.

One approach to the problem of rectal toxicity is to push the rectum away from the prostate, increasing the space between the 2 organs and reducing the radiation dose to the anterior rectal wall. A variety of biomaterials, including collagen, polyethylene glycol (PEG) hydrogels, and absorbable balloons have been evaluated as a means to reduce rectal radiation exposure. The SpaceOAR System is the first PEG hydrogel that was cleared by the FDA specifically for use during RT of the prostate. The chemical composition of the SpaceOAR is similar to a PEG-based hydrogel that is FDA approved as a dural sealant. Hydrodissection is achieved with saline between the retroprostatic (Denovilliers') fascia and the anterior rectal wall using a transperineal approach. Once the needle placement is confirmed, 2 solutions in a 2-channel syringe are injected into the perirectal space. The hydrogel then polymerizes to form a soft mass. The hydrogel maintains the space for approximately 3 months, the duration of radiotherapy, and is completely absorbed by 12 months. The PEG hydrogel may be injected at the same time as the placement of fiducial markers in the prostate.

The question addressed in this evidence review is: Does the use of a hydrogel perirectal spacer improve the net health outcome in patients with prostate cancer who are being treated with external beam radiotherapy (EBRT)?

The following PICO was used to select literature to inform this review.

**Patients**
The relevant population of interest is men with prostate cancer who are being treated with EBRT or brachytherapy.

**Interventions**
The therapy being considered is a polyethylene glycol hydrogel (SpaceOAR System) that is injected between the prostate and rectum. The gel increases the space between the rectum and the prostate to about 12 mm. It maintains space for approximately 3 months and then is gradually absorbed and cleared.

**Comparators**
The following therapies are currently being used to make decisions about the treatment of prostate cancer: EBRT without a spacer. Rectal toxicity of Grade 2 or greater was reported to be 1.5% at 3 to 15 months following moderate hypofractionated EBRT, indicating a number needed to treat (NNT) of 68 to avoid 1 case of clinically significant rectal toxicity.\(^3\)

**Outcomes**
The outcomes of interest are symptoms of rectal toxicity, adverse events, and QOL. Rectal toxicity according to the Common Terminology Criteria for Adverse Events is classified as Grade 0: no symptoms or complications; Grade 1: mild symptoms are present but no intervention is required; Grade 2: a moderate event affecting daily activities, intervention is required; Grade 3: a severe event that requires hospitalization; Grade 4: a life-threatening event; and Grade 5: death. Clinically significant rectal toxicity requiring intervention is considered to be Grade 2 or higher.
Prostate cancer-specific QOL can be measured by the Expanded Prostate Cancer Index Composite health-related QOL questionnaire, with 5- and 10-point thresholds for minimum clinically important differences (MCID). Skolarus et al (2015) reported the bowel and vitality/hormonal domains had an MCID 4-6 point range, while the sexual domain had an MCID range of 10-12. Urinary incontinence had a greater MCID range (6-9) compared with the urinary irritation/obstruction domain (5-7).

Although considered a surrogate outcome, studies may also report estimated radiation doses to the rectum from radiation planning, with the rectal volume predicted to receive a radiation dose over the threshold (eg, rectal volume receiving 70 Gray [Gy]).

A beneficial outcome would be reduced rectal toxicity and reduced impairment in QOL following radiotherapy.

A harmful outcome would be adverse effects of the spacer, spacer insertion, or spacer absorption.

Follow-up should be for at least 2 years since the median time for the occurrence of radiation toxicity is 18 months.

**Study Selection Criteria**

To assess efficacy outcomes, we sought comparative controlled prospective trials, with a preference for RCTs. To assess long-term outcomes and adverse effects, we sought single-arm studies that capture longer periods of follow-up and/or larger populations.

**Randomized Controlled Trials**

Results from the pivotal RCT for the SpaceOAR System were published by Mariados et al (2015), with 3-year follow-up published by Hamstra et al (2017) (see Table 2). A total of 222 men were randomized 2:1 to the spacer or control group. All men were implanted with fiducial markers for image-guided intensity-modulated radiation therapy and received 79.2 Gy in 1.8-Gy fractions to the prostate. The primary outcome was the percent of the rectal volume receiving 70 Gy in dose planning studies, which was 3.3% with the peri-rectal spacer and 11.7% in the control group (p<0.001, see Table 3). Blinded adjudication identified no spacer-related adverse events. Grade ≥ 1 adverse events were similar between the groups at 6 and 15 months but were reduced at 3 years in the group with the SpaceOAR System (2% vs. 9%, p<0.03) with an NNT of 14.3. Fewer patients reported a clinically significant decline in bowel or urinary-related QOL with an NNT of 6.3 and 6.7, respectively (see Table 2). Patients were not blinded to treatment at the 3 year follow-up.

Table 2. Summary of Key RCT Characteristics

<table>
<thead>
<tr>
<th>Study; Trial</th>
<th>Countries</th>
<th>Sites</th>
<th>Dates</th>
<th>Participants</th>
<th>Interventions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mariados et al, (2015)</td>
<td>U.S.</td>
<td>20</td>
<td>2012-2013</td>
<td>222 patients with clinical stage T1 or T2 prostate cancer with Gleason score of ≤7, PSA ≤20 ng/ml, Zubrod performance status 0 to 1, who were planning to undergo IG-IMRT</td>
<td>149 patients who received perirectal injection of a hydrogel between the prostate and rectum prior to IG-IMRT</td>
</tr>
<tr>
<td>Hamstra et al (2017)</td>
<td>U.S.</td>
<td>20</td>
<td>2012-2013</td>
<td>73 patients who received only fiducial markers inserted in the prostate prior to IG-IMRT (79.2 Gy in 1.8-Gy fractions)</td>
<td>73 patients who received only fiducial markers inserted in the prostate prior to IG-IMRT (79.2 Gy in 1.8-Gy fractions)</td>
</tr>
</tbody>
</table>
Gy: gray; PSA: prostate-specific antigen; IG-IMRT: image-guided intensity-modulated radiation therapy; RCT: randomized controlled trial.

Table 3. Summary of Key RCT Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Rectal Volume Receiving ≥70 Gy</th>
<th>Percent of Patients with ≥25% Reduction in Rectal Volume Receiving ≥70 Gy</th>
<th>Grade ≥ 1 Rectal or Procedure Adverse Events at 6 mo</th>
<th>Patients with Grade ≥ 1 Late Toxicity</th>
<th>10 Point Decline in Bowel QOLa</th>
<th>10 to 12 Point Decline in Urinary QOL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mariados et al, (2015)</td>
<td>N 219</td>
<td>97.3%</td>
<td>34.2%</td>
<td>219</td>
<td>11.6%</td>
<td>10%</td>
</tr>
<tr>
<td></td>
<td>Hydrogel spacer</td>
<td>3.3%</td>
<td></td>
<td>145 (98.0%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>11.7%</td>
<td>NA</td>
<td>31.5%</td>
<td>21.4%</td>
<td>12%</td>
</tr>
<tr>
<td></td>
<td>P-Value</td>
<td>&lt;0.001</td>
<td></td>
<td>0.70</td>
<td>0.044</td>
<td></td>
</tr>
<tr>
<td>Hamstra et al (2017)</td>
<td>N 140</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Hydrogel spacer</td>
<td>2% (1 to 6)</td>
<td>5%</td>
<td>21%</td>
<td>23%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Control</td>
<td>9% (4 to 20)</td>
<td></td>
<td>0.03</td>
<td>0.02</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>OR (95% CI)</td>
<td></td>
<td></td>
<td>0.28</td>
<td>(0.13 to 0.63)</td>
<td>0.31</td>
</tr>
<tr>
<td></td>
<td>NNT</td>
<td>14.3</td>
<td>6.3</td>
<td>6.7</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CI: confidence interval; Gy: gray; NA: not applicable; NNT: number needed to treat; OR: odds ratio; QOL: quality of life; RCT: randomized controlled trial.

a Expanded Prostate Cancer Index Composite health-related QOL questionnaire

b Difference between groups due primarily to grade 1 toxicity. There was one case of grade 3 toxicity in the control group and no cases of grade 4 toxicity.

c There was no grade ≥ 2 rectal toxicity in the spacer arm compared with 6% (95% CI, 2% to 17%, p<0.015) in the control arm.

Limitations in relevance and design and conduct are shown in Tables 4 and 5. The primary limitations in relevance was the population, which was restricted for this pivotal controlled trial. The primary limitations in design and conduct were the lack of investigator blinding and the loss to follow-up at 3 years.

Table 4. Relevance Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Populationa</th>
<th>Interventionb</th>
<th>Comparatork</th>
<th>Outcomesd</th>
<th>Follow-Upa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mariados et al, (2015)</td>
<td>4. Patients with prostate volumes &gt;80 mL, extracapsular extension, or prior radiation or surgery were excluded</td>
<td></td>
<td></td>
<td></td>
<td>1, 2. 15-month follow-up; 3-year follow-up was reported by Hamstra et al 2017</td>
</tr>
<tr>
<td>Hamstra et al (2017)</td>
<td>4. Patients with prostate volumes &gt;80 mL, extracapsular extension, or prior radiation or surgery were excluded</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.

a Population key: 1. Intended use population unclear; 2. Clinical context is unclear; 3. Study population is unclear; 4. Study population not representative of intended use.
b Intervention key: 1. Not clearly defined; 2. Version used unclear; 3. Delivery not similar intensity as comparator; 4. Not the intervention of interest.

c Comparator key: 1. Not clearly defined; 2. Not standard or optimal; 3. Delivery not similar intensity as intervention; 4. Not delivered effectively.

d Outcomes key: 1. Key health outcomes not addressed; 2. Physiologic measures, not validated surrogates; 3. No CONSORT reporting of harms; 4. Not establish and validated measurements; 5. Clinical significant difference not prespecified; 6. Clinical significant difference not supported.

e Follow-Up key: 1. Not sufficient duration for benefit; 2. Not sufficient duration for harms.

Table 5. Study Design and Conduct Limitations

<table>
<thead>
<tr>
<th>Study</th>
<th>Allocationa</th>
<th>Blindingb</th>
<th>Selective Reportingc</th>
<th>Data Completenessd</th>
<th>Powere</th>
<th>Statisticalf</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mariados et al, (2015)²</td>
<td></td>
<td>1, 3. Not blinded to treatment assignment</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hamstra et al (2017)⁵</td>
<td></td>
<td>1, 2, 3. Not blinded to treatment assignment</td>
<td>1. 3 yr data were available for only 63% of patients</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The study limitations stated in this table are those notable in the current review; this is not a comprehensive limitations assessment.


d Data Completeness key: 1. High loss to follow-up or missing data; 2. Inadequate handling of missing data; 3. High number of crossovers; 4. Inadequate handling of crossovers; 5. Inappropriate exclusions; 6. Not intent to treat analysis (per protocol for noninferiority trials).

e Power key: 1. Power calculations not reported; 2. Power not calculated for primary outcome; 3. Power not based on clinically important difference.

f Statistical key: 1. Analysis is not appropriate for outcome type: (a) continuous; (b) binary; (c) time to event; 2. Analysis is not appropriate for multiple observations per patient; 3. Confidence intervals and/or p-values not reported; 4. Comparative treatment effects not calculated.

Fischer-Valuck et al (2017) reported secondary analysis of magnetic resonance imaging for the 149 patients enrolled in the pivotal trial who received the hydrogel spacer.² The spacer was symmetrically placed at midline for 71 (47.7%) patients, with 78 (50.9%) having some asymmetry and 3 (2.0%) with greater than 2 cm lateral distribution. The greater the asymmetry the lower the decrease in rectal radiation, although all but 4 patients achieved a 25% or greater reduction in rectal volume receiving 70 Gy. Infiltration of the rectal wall occurred in 9 (6%) patients but was not associated with procedure-related adverse events or acute or late rectal toxicity.

Systematic Reviews

Forero et al (2018) conducted a systematic review for the Technology Assessment Unit of the McGill University Health Centre.³ They included the RCT reported by Mariados et al (2015) and Hamstra et al (2017) and 5 non-randomized comparative studies (3 from the same institution) that evaluated the effect of SpaceOAR on rectal radiation exposure, rectal toxicity, or QOL (See Table 6). Four studies found that placement of SpaceOAR resulted in lower rectal radiation exposure, but 3 studies that assessed rectal toxicity did not show important differences between the SpaceOAR and control groups. The RCT and 3 observational studies that evaluated QOL found no major differences between the SpaceOAR and control groups in the first year of follow-up. Longer-term results were inconsistent across studies. All of the studies had major limitations. The review concluded that while SpaceOAR does reduce rectal radiation exposure, it is unclear whether this impacts rectal toxicity and QOL.³
Table 6. Characteristics of Included Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Control</th>
<th>N SpaceOAR/controls</th>
<th>Treatment</th>
<th>Radiation Dose - Gy</th>
<th>Follow-up mo</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mariados et al (2015)</td>
<td>RCT</td>
<td>Blinded through 15 mo</td>
<td>149/73</td>
<td>IMRT</td>
<td>79.2</td>
<td>15 and 36</td>
<td>x</td>
</tr>
<tr>
<td>Hamstra et al (2017)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Whalley et al (2016)</td>
<td>Prospective cohort</td>
<td>Historical controls</td>
<td>30/110</td>
<td>IMRT</td>
<td>80</td>
<td>28</td>
<td>x</td>
</tr>
<tr>
<td>Te Velde et al (2017)</td>
<td>Retrospective</td>
<td>Concurrent controls</td>
<td>65/60</td>
<td>IMRT</td>
<td>81</td>
<td>4</td>
<td>x</td>
</tr>
<tr>
<td>Pinkawa et al (2012)</td>
<td>Retrospective</td>
<td>Matched controls</td>
<td>28 vs 28 vs 28</td>
<td>IMRT</td>
<td>78 vs 76 vs 70</td>
<td>3</td>
<td>x</td>
</tr>
<tr>
<td>Pinkawa et al (2017)</td>
<td></td>
<td></td>
<td>101/66</td>
<td>IMRT</td>
<td>76-80</td>
<td>12</td>
<td>x</td>
</tr>
<tr>
<td>Pinkawa et al (2017)</td>
<td></td>
<td></td>
<td>54/60</td>
<td>IMRT</td>
<td>76-78</td>
<td>72</td>
<td>x</td>
</tr>
</tbody>
</table>

Gy: gray; IMRT: intensity-modulated radiation therapy; RCT: randomized controlled trial.

Te Velde et al (2019) published 3-year follow-up of patients from their 2017 report (See Table 6). Patients were excluded from analysis if their follow-up evaluations were not completed. The cumulative incidence of Grade 1 diarrhea (6.2% vs. 21.4%, p=0.016) and Grade 2 proctitis (0% vs. 7.1%, p=0.043) were statistically lower in the SpaceOAR group, but these outcome measures were not significantly different when assessed at 3 years after radiotherapy. The clinical significance of a difference between groups of Grade 1 diarrhea at any time during follow-up, but not at final follow-up, suggests that mild rectal toxicity resolves by 3 years. Fecal incontinence and hemorrhoids were not significantly different at any time point. In addition to questions of clinical significance, this study is limited by potential for selection bias and detection bias in this unblinded non-randomized study. All patients had been offered the SpaceOAR, but only patients with private insurance underwent the procedure, raising the possibility of differences in health or other personal factors between patients who had received the SpaceOAR and those who had not.

Studies Not Included in Systematic Reviews

Chao et al (2019) reported a retrospective analysis of patients with intermediate and high-risk prostate cancer who were treated with both high dose rate brachytherapy and EBRT. Outcomes from consecutive patients treated with the hydrogel spacer between 2014 and 2017 were compared with consecutive patients treated between 2010 and 2013 without a spacer (see Table 7). Results are shown in Table 8. Rectal dose was significantly reduced. Group differences in Grade 1 or greater early gastrointestinal toxicity approached statistical significance (13.3% vs. 30.8%, p=0.05), but there was no significant difference in early Grade 2 toxicity (0% vs. 1.5% in...
controls, p=0.48) or in late Grade 1 toxicity (0% vs. 7.7% without a spacer, p=0.11). There were no cases of late Grade 2 toxicity and no significant differences between the groups in genitourinary toxicity.

Table 7. Characteristics of Non-Randomized Comparative Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Control</th>
<th>Participants</th>
<th>N SpaceOAR/c</th>
<th>Treatment</th>
<th>Radiatio n Dose - Gy</th>
<th>Follow up mo</th>
<th>Outcome Measures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chao et al (2019)</td>
<td>Retrospective analysis of consecutive patients</td>
<td>Consecutive patients treated between 2010 - 2013</td>
<td>Patients with intermediate and high-risk prostate cancer treated between 2010-2017</td>
<td>32/54</td>
<td>HDR brachytherapy and EBRT</td>
<td>Brachytherapy: 16 54.1 EBRT: 54.1</td>
<td>3 x x x</td>
<td>Rectal Dose - Volume</td>
</tr>
</tbody>
</table>

EBRT: external beam radiotherapy; Gy: gray; HDR: high dose rate.

Table 8. Summary of Non-Randomized Comparative Study Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Rectal Dose-Volume</th>
<th>Early Gastrointestinal Toxicity</th>
<th>Late Gastrointestinal Toxicity</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>&gt; Grade 1</td>
<td>Grade 2</td>
</tr>
<tr>
<td>Chao et al (2019)</td>
<td>Median V75 (cc)</td>
<td>13.3%</td>
<td>0%</td>
</tr>
<tr>
<td>SpaceOAR</td>
<td>0 (0-0.22)</td>
<td>30.8%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Control</td>
<td>0.45 (0-1.46)</td>
<td>0.05</td>
<td>0.48</td>
</tr>
<tr>
<td>p-Value</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Summary of Evidence

For individuals who have prostate cancer and are undergoing radiation therapy who receive a hydrogel spacer, the evidence includes a pivotal RCT with a 3-year follow-up, observational studies, and systematic reviews of these studies. Relevant outcomes include symptoms, quality of life, and treatment-related morbidity. The combined evidence indicates that the hydrogel spacer can reduce the radiation dose to the rectum with a statistically significant decrease in Grade 1 or greater late toxicity and a number needed to treat of 14.3. There were few events of greater than Grade 1 toxicity in either group, and the number needed to treat for a reduction in clinically significant Grade 2 toxicity has been reported as 68. Patient-reported declines in rectal and urinary quality of life at 3 years were statistically lower in the spacer group and met the threshold for a clinically significant difference, although patients were not blinded to treatment at the longer-term follow-up. The number needed to treat for late improvement in rectal and urinary quality of life were 6.3 to 6.7, respectively. Limitations to the study include the lack of blinding and the exclusion of patients who might be at greater risk of rectal toxicity. Evidence from observational studies is inconclusive, and potential benefits of the hydrogel spacer must be balanced against the risks of an additional procedure. Additional study is needed to corroborate the findings of the pivotal RCT, to identify the factors that increase the risk of rectal toxicity, and
to determine who is likely to benefit from the use of a spacer. The evidence is insufficient to
determine the effects of the technology on health outcomes.

**Practice Guidelines and Position Statements**

**National Comprehensive Cancer Network**
The National Comprehensive Cancer Network (V4:2019) provides the following recommendation
in principles of radiation therapy, "Perirectal spacer materials may be employed when the
previously mentioned techniques [highly conformal RT, photon or proton beam, brachytherapy
boost] are insufficient to improve oncologic cure rates and/or reduce side effects due to anatomic
geometry or other patient-related factors, such as medication usage and/or comorbid conditions.
Patients with obvious rectal invasion or visible T3 and posterior extension should not undergo
perirectal spacer implantation."15

**National Institute for Health and Care Excellence**
The National Institute for Health and Care Excellence (2017) published guidance on the
biodegradable spacer16. The National Institute for Health and Care Excellence concluded that
"current evidence on the safety and efficacy of insertion of a biodegradable spacer to reduce
rectal toxicity during radiotherapy for prostate cancer is adequate to support the use of this
procedure."

**American Society of Clinical Oncology, the American Urological Association, and the
American Society for Radiation Oncology**
The American Society of Clinical Oncology, the American Urological Association, and the American
Society for Radiation Oncology (2018) published a joint guideline on hypofractionated radiation
therapy for localized prostate cancer.17. The guideline recommends that men be counseled about
the small increased risk of acute gastrointestinal toxicity with hypofractionation. "Moderately
fractionated EBRT has a similar risk of acute and late genitourinary and late GI toxicity compared
with conventionally fractionated EBRT. However, physicians should discuss the limited follow-up
beyond 5 years for most existing RCTs [randomized controlled trials] evaluating moderate
hypofractionation." This was a strong recommendation based on high-quality evidence and 100%
consensus.

**U.S. Preventive Services Task Force Recommendations**
Not applicable.

**Ongoing and Unpublished Clinical Trials**
Some currently unpublished trials that might influence this review are listed in Table 9.

<table>
<thead>
<tr>
<th>NCT No.</th>
<th>Trial Name</th>
<th>Planned Enrollment</th>
<th>Completion Date</th>
</tr>
</thead>
<tbody>
<tr>
<td>NCT01999660a</td>
<td>Prospective National Post-marketing Surveillance for the Investigation of the Efficacy and Safety of SpaceOAR™ to Maintain Space Between the Rectum and Prostate During Radiation Therapy</td>
<td>250</td>
<td>Jan 2019 (status unknown last update posted Feb 2015)</td>
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</tbody>
</table>

NCT: national clinical trial.

a Denotes industry-sponsored or cosponsored trial.
CODING

The following codes for treatment and procedures applicable to this policy are included below for informational purposes. Inclusion or exclusion of a procedure, diagnosis or device code(s) does not constitute or imply member coverage or provider reimbursement. Please refer to the member’s contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

CPT/HCPCS

55874 Transperineal placement of biodegradable material, peri-prostatic, single or multiple injection(s), including image guidance, when performed

Diagnoses

Experimental / Investigational for all diagnoses related to this medical policy.

REVISIONS


REFERENCES


